REMARKS

Reconsideration of the application, as amended, is respectfully requested in view of the following remarks.

In view of the informality noted by the Office, claims 2 and 11 have been canceled without prejudice.

The Office has rejected claims 1-13 and 15-17 under 35 U.S.C. 103(a) as being unpatentable over Reimer et al. (WO 01/37850) in view of O'Callaghan et al. (WO 93/04593). According to the Office it would have been obvious to use the hypoallergenic whey protein hydrolysates taught by O'Callaghan in place of the sweet or acid whey protein in the method of treating diabetes as taught by Reimer.

It is submitted that there is no incentive for a person of average skill in the art to combine the teachings of Reimer with those of O'Callaghan. Reimer teaches to treat type II diabetes with the help of a milk protein hydrolysate which is capable of inducing release of GLP-1. As explained on page 2, lines 16-18, "increasing insulin secretion is a key goal in the treatment of type II diabetes and stimulation of endogenous release of GLP-1 is a potential/prospective alternative to intravenous administration." In other words, the capability of a milk protein hydrolysate to induce release of GLP-1 is a critical feature of the teachings of Reimer. In addition, it is noted that Reimer teaches that caseinoglycomacropeptide (CGMP) is largely responsible for the GLP-1 inducing effect of certain milk protein hydrolysates.

O'Callaghan relates to infant formulae and special dietetic foodstuffs that contain a hypoallergenic whey protein hydrolysate. If, as implicitly asserted by the Office, a skilled person would be led to replace the milk protein hydrolysate in the method of

treating type II diabetes taught by Reimer with a suitable hypoallergenic hydrolysate, such person would only consider candidates that are capable if inducing GLP-1 release. The Office points too no data or suggestions in O'Callaghan which imply that the hypoallergenic whey protein hydrolysate described therein are capable of inducing GLP-1 release. Therefore, it would require the benefit of hindsight from the present application to argue that the hypoallergenic whey protein hydrolysates of O'Callaghan could suitably be employed in the treatment of type II diabetes as taught by Reimer.

Applicants submit that knowing that the peptide part of CGMP, the essential component in the milk protein hydrolysates of Reimer, has a molecular weight of 8,000 Dalton, but that the molecular weight of the glycosylated molecule can range from 25,000 to 30,000 Daltons (see the attached Davisco publication found on the Internet), a skilled person would expect the hypoallergenic whey hydrolysates of O'Callaghan to be largely ineffective in the method taught by Reimer. The molecular weight distributions of the hypoallergenic whey protein hydrolysates depicted in the Tables 2, 4, 6, 8 and 10 contain only a minor fraction of material having a molecular weight in excess of 5,000 Daltons. Clearly, in the whey protein hydrolysates of O'Callaghan CGMP content has been reduced substantially as a result of proteolysis and subsequent microfiltration, meaning that a skilled person would not contemplate using these hypoallergenic whey protein hydrolysates in the treatment of type II diabetes as taught by Reimer.

With respect to the Office's implicit assertion that treatment of type II diabetes inherently corresponds with the method defined in present, applicants submit as follows.

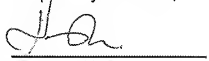
Finally, it is noted that present claim 1 recites that the whey protein hydrolysate contains 30-45 wt.% of material having a molecular weight of at least 10,000 Daltons. However, the hypoallergenic whey protein hydrolysates described in Tables 2, 4, 6, 8 and 10 contain 2.3-11.2 wt.% of material having a molecular weight of at least 5,000 Daltons. Consequently, even if a skilled person were to employ a hypoallergenic whey protein

hydrolysate taught by O'Callaghan in the method as taught by Reimer, the Office points to no teaching by O'Callaghan of the presently recited range of higher molecular weights, so the cited references would not lead such person to the subject matter of present claim 1.

Applicants are willing to file a terminal disclaimer upon indication of allowable subject matter.

In view of the foregoing, it is respectfully requested that the application, as amended, be allowed.

Respectfully submitted,



Gerard J. McGowan, Jr.
Registration No. 29,412
Attorney for Applicant(s)

GJM/mpk
(201) 894-2297

DAVISCO
FOODS INTERNATIONAL, INC.

SPECIALTY PRODUCTS

- BIPRO
- BIOZATE
- ALPHA-LACTALBUMIN
- GMP

ION-EXCHANGE VS MICROFILTRATION
Adobe PDF File (318KB)

For sales information about our products: Please contact the Davisco Sales Office at 952-914-0400 or 1-800-757-7611, or by e-mail.

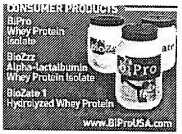
PRODUCT CHARACTERISTICS | APPLICATIONS | SPECIFICATIONS
NUTRIENT INFO/AMINO ACID PROFILES | CONTACT SALES OFFICE | REQUEST SAMPLE

PRODUCT CHARACTERISTICS

- **Highly purified source of glycomacropeptide**
- **Low in the amino acid phenylalanine (Phe)**
- **May stimulate the body to produce CCK – the protein released after eating that gives a sense of satiety**
- **Role in tooth remineralization and dental plaque reduction**
- **Fully soluble**
- **Bland, neutral taste**
- **Lactose free**

APPLICATIONS

Glycomacropeptide (GMP) is a highly bioactive whey protein with superior purity. Davisco Foods International, Inc. has developed a unique process by which a purified



Download
a FREE copy of
Adobe Acrobat Reader

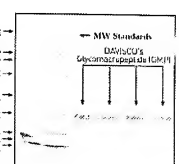
- Beverages
- Nutrition bars
- Medical foods (PKU)
- Diet foods
- Oral care products
- Dietary supplements

PRODUCT SPECIFICATIONS

NUTRIENT INFO/
AMINO ACID PROFILES

form of glycomacropeptide is isolated from the whey after cheesemaking. The result is a light colored, mild tasting, free flowing powder ideal for usage in both functional foods and beverages, and dietary supplements.

GMP is a casein-derived whey peptide. When milk is treated with chymosin during cheesemaking, the milk protein (k-casein) is hydrolyzed into two peptides. The larger peptide containing the amino acid residues 1-105 is called para-k-casein, which becomes part of the cheese curd, while the smaller peptide containing amino acid residues 106-169 becomes soluble and part of the whey. The peptide is relatively small, with a molecular weight of 8000 Daltons, however due to glycosylation its actual size can range from 25000 to 30000 Daltons. There are two major variants of GMP, variant A and variant B, which differ in two amino acids. Different abbreviations are used to identify GMP, but all refer to the same molecule found in whey. CMP is the abbreviation for caseinmacropeptide, cGMP is used as a more descriptive designation of casein-glycomacropeptide. It is sometimes also referred to as CDP (casein-derived peptide) or CGP (caseinglycopeptide) to identify its origin.



GMP AND SIALIC ACID

GMP has many unique characteristics compared to other whey proteins. The "glyco"

portion of its name refers to the saccharide groups that are attached to the peptide backbone of the molecule. Researchers have identified five different heterogeneous sugar chains related to GMP derived from mature bovine milk. The most prominent of these is *N*-acetylneuraminic acid, commonly known as sialic acid. The glycolysation or the amount of sialic acid of GMP varies widely and is affected by the manufacturing process. Davisco's GMP has a high level of purity and contains approximately 8.5% sialic acid on a GMP basis.

GMP AND AMINO ACIDS

GMP differs from other whey proteins in its amino acid profile. The uniqueness of GMP is the low levels of aromatic amino acids (phenylalanine, tryptophan, and tyrosine). GMP also has relatively high amounts of branched chain amino acids (isoleucine and valine). The combination of low aromatic amino acids and high BCAAs allows GMP to be an ideal ingredient in nutritional formulations for people suffering from hepatic diseases. The low level of phenylalanine in Davisco's GMP also makes it a highly desirable nitrogen source in the special diets formulated for phenylketoneuria patients.

PKU

Phenylketonuria, or PKU is a rare, hereditary, metabolic disorder. PKU is inherited as an autosomal recessive trait. In the United States, about one in every 19,000 births inherit this metabolic abnormality.

For a person with normal metabolism, phenylalanine is an essential amino acid that must be provided in the diet. However, in a phenylketonuric, dietary phenylalanine cannot be metabolized in a normal fashion because of a missing enzyme. As a result, a person with PKU consuming a normal diet would accumulate high levels of phenylalanine and its derivatives, causing the toxicity to the central nervous system and possible brain damage. Special low-phenylalanine diets that provide adequate protein are essential for phenylketonurics. Davisco's purified GMP is an ideal ingredient in such diets since it contributes a minimal amount of phenylalanine.

AMINO ACID PROFILE – DAVISCO'S GMP

Amino Acid	Grams per 100g powder
Alanine	5.5
Arginine	0.5
Aspartic Acid	8.6
Cysteine	0.1
Glutamic Acid	20.5
Glycine	1.1

Histidine*	0.3
Isoleucine*‡	10.1
Leucine*‡	2.6
Lysine*	5.9
Methionine*	1.8
Phenylalanine*	0.5
Proline	12.5
Serine	6.1
Threonine*	15.8
Tryptophan	0.0
Tyrosine*	0.1
Valine*‡	8.0

* Essential Amino Acid
‡ Branched Chain Amino Acid

DENTAL CARIES AND PLAQUE REDUCTION

Plaque and dental caries are a result of microbial adhesion and activity on the dental surface. GMP has been shown to have a protective effect by reducing the binding of bacteria, such as the *Streptococcus* species,on a saliva-covered tooth model and the inner lining of the cheek. Scientists believe that by inhibiting the cariogenic bacteria, GMP reduces dental plaque and caries.[1,2,3]

INFANT FORMULATIONS

Bifidobacteria inhibit growth of pathogenic bacteria in the GI tract and are important for the protection of infants from gastrointestinal diseases. Although many factors contribute to the colonization and growth of bifidobacteria, various studies seem to indicate the GMP may promote the growth of these beneficial organisms.8,9 Additional evidence demonstrates that GMP has immuno-modulatory effects and affords a passive defense mechanism to newborns.[4,5]

References

[1]Ainutis, W. R. 2004. Bioactive Properties of Milk Proteins with Particular Focus on Anticariogenesis. *Journal of Nutrition* 134: 989S-95S.

[2]Janer, C., J. Díaz, C. Peláez, and T. Requena. 2004. The Effect of Caseinomacropeptide and Whey Protein Concentrate on *Streptococcus*

Mutans Adhesion to Polystyrene Surfaces and Cell Aggregation. *Journal of Food Quality* 27: 233-8.

[3]Neeser, J. R., A. Chambaz, S. Del Vedovo, M. J. Prigent, and B. Guggenheim. 1988. Specific and Nonspecific Inhibition of Adhesion of Oral Actinomyces and Streptococci to Erythrocytes and Polystyrene by Caseinoglycopeptide Derivatives. *Infection and Immunity* 56(12): 3201-8.

[4]Azuma, N., K. Yamauchi, and T. Mitsuoka. 1984. Bifidus Growth-Promoting Activity of a Glycomacropeptide Derived From Human K-Casein. *Agricultural and Biological Chemistry* 48(8): 2159-62.

[5]Bezkorovainy, A., D. Grohlich, and J. H. Nichols. 1979. Isolation of a Glycopolypeptide Fraction with Lactobacillus Bifidus Subspecies Pennsylvanicius Growth-Promoting Activity From Whole Human Milk Casein. *American Journal of Clinical Nutrition* 32: 1428-32.

11000 West 78th Street, Suite 210, Eden Prairie, MN 55344 Tel. 952-914-0400 FAX: 952-914-0887